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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/509,648	10/05/2000	Mark F. Charette	CIBT-P01-569	7787

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EXAMINER
BUNNER, BRIDGET E

ART UNIT	PAPER NUMBER
1647	20

DATE MAILED: 08/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/509,648	CHARETTE ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 March 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *13-15,20,21 and 27-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,16-19 and 22-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-32* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's continued traversal of the Restriction requirements set forth in Paper No. 10 (18 December 2001) and Paper No. 14 (28 June 2002) (14 June 2002) appears moot since the restriction requirement was made final in the previous Office Action (Paper No. 17, 13 November 2002). If Applicant wishes to pursue the matter further, a petition should be filed in accordance with 37 CFR 1.144.

Status of Application, Amendments and/or Claims

The amendment of 11 March 2003 (Paper No. 19) has been entered in full. Claims 1, 4, 11-12, and 16-17 are amended.

This application contains claims 13-15, 20-21, and 27-32 drawn to an invention nonelected with traverse in Paper No. 13 (18 April 2002) and Paper No. 15 (05 August 2002). A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-12, 16-19, and 22-26 are under consideration in the instant application. The claims also read upon the following species: Alzheimer's disease from the disorder group, cytokine antagonist from the agent capable of releasing morphogen activity group, 2-p-bromocinnamylaminoethyl)-isoquinolinesulfonamide from the protein kinase A inhibitor group, SEQ ID NO: 2 from the morphogen amino acid sequence group, OP-1 from the morphogen group, and retinoid receptor from the molecule that binds an endogenous ligand group.

Withdrawn Objections and/or Rejections

1. The objections to the specification at pg 3-4 of the previous Office Action (Paper No. 17, 13 November 2002) are *withdrawn in part* in view of the submitted abstract and amended specification (Paper No. 19, 11 March 2003). Please see section on Specification, below.

2. The objections to claim 8-9, 11, 16-17, 19, and 26 at pg 4 of the previous Office Action (Paper No. 17, 13 November 2002) are *withdrawn in part* in view of amended claim 11(Paper No. 19, 11 March 2003). Please see section on Claim Objections, below.

3. The rejection to claim 17 under 35 U.S.C. § 112, first paragraph (new matter) as set forth at pg 8 of the previous Office Action (Paper No. 17, 13 November 2002) is *withdrawn* in view of the amended claim (Paper No. 19, 11 March 2003).

4. The rejections to claims 1-12, 16-19, and 22-26 under 35 U.S.C. 112, second paragraph, as set forth at pg 8-9 of the previous Office Action (Paper No. 17, 13 November 2002) are *withdrawn in part* in view of the amended claims (Paper No. 19, 11 March 2003). Please see section on 35 U.S.C. 112, second paragraph below.

Specification

5. The disclosure is objected to because of the following informalities:

5a. Patent applications are referenced throughout the disclosure (pg 1, lines 14-15; pg 21, lines 8-9; pg 25, line 25; pg 35, line 11). The status of the applications must be updated. The basis for this objection is set forth at pg 4 of the previous Office Action (Paper No. 17, 13 November 2002).

Applicant's arguments (Paper No. 19, 11 March 2003), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant asserts that the specification has been amended to obviate this rejection. Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, not all of the patent applications have been updated. See for example, USSN 08/404,113 (pg 1), USSN 08/260,675 (pg 1), USSN 08/292,782 (pg 25), USSN 08/958,463 (pg 35), and USSN 08/937,755 (pg 35). It is noted to Applicant that if there are applications cited in the specification that are still pending, this objection will be maintained until the status of those cases changes or allowable subject matter is identified in the instant application.

Claim Objections

6. Claims 8-9, 11, 16-17, 19, 26 are objected to because of the following informalities:

6a. Claims 8-9, 16-17, 19, and 26 recite non-elected species. The basis for this objection is set forth at pg 4 of the previous Office Action (Paper No. 17, 13 November 2002).

Applicant's arguments (Paper No. 19, 11 March 2003), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant asserts that claims 8-9, 11, 16-17, 19, and 26 are generic claims linking elected and non-elected species. Applicant cites MPEP 809.02(a) and emphasizes that the burden is on the Examiner to examine these generic claims throughout their scope, together with any claims dependent thereon drawn to non-elected species or inventions, rather than for Applicant to limit the scope of the generic claims to conform to the scope of any species or inventions listed in a Restriction requirement.

Applicant's arguments have been fully considered but are not found to be persuasive. As indicated in the previous Office Action (Paper No. 17, 13 November 2002), the restriction requirement was made final. The Examiner explained that non-elected species would not be

searched because an art search for every species would not overlap. Each disorder and molecule is unique, requiring a unique search of the prior art. Searching all of the species in a single patent application would provide an undue search burden on the Examiner and the USPTO's resources because of the non-coextensive nature of these searches. Following Applicant's species election, the claims were examined to the extent that they read upon the elected species. If Applicant wishes to pursue the matter further, a petition should be filed in accordance with 37 CFR 1.144.

35 USC § 112, first paragraph

7. Claims 1-12, 16-19, and 22-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of reducing leukemia inhibitory factor (LIF)-induced dendritic retraction comprising adding an antibody to gp130 to sympathetic neurons *in vitro* that have been treated with LIF and osteogenic protein-1 (OP-1) and wherein said antibody reduces LIF-induced dendritic retraction, does not reasonably provide enablement for a method for potentiating morphogen activity, a method for promoting neuronal cell growth, a method for treating a disorder characterized by neuronal cell loss, or a method for treating a neurodegenerative disorder comprising administering to a mammal a composition comprising a molecule that overcomes morphogen inhibition. Additionally, the specification is enabling for a method of reducing ciliary neurotrophic factor (CNTF)-induced dendritic retraction comprising adding phosphatidylinositol-specific phospholipase C (PI-PLC) to sympathetic neurons *in vitro* before the neurons have been treated with CNTF and osteogenic protein-1 (OP-1) and wherein said PI-PLC reduces CNTF-induced dendritic retraction. The specification is also enabling for a method of reducing the inhibitory effects of LIF on OP-1 stimulated dendritic growth comprising

adding an anti-LIF antibody to sympathetic neurons *in vitro* that have been treated with LIF and OP-1 and wherein said antibody reduces the inhibition of LIF on OP-1 stimulated dendritic growth. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-12, 16-19, and 22-26 are directed to a method for potentiating morphogen activity comprising administering to a mammal a composition comprising a molecule that overcomes morphogen inhibition, thereby potentiating morphogen activity. The claims recite a method for promoting neuronal cell growth and a method for treating a disorder characterized by neuronal cell loss comprising administering to a mammal a composition comprising a molecule that overcomes morphogen inhibition, thereby to potentiate growth-promoting effects of endogenous morphogens. The claims recite a method for treating a neurodegenerative disorder comprising administering to a mammal a composition comprising a molecule that overcomes morphogen inhibition, thereby treating a neurodegenerative disorder. The claims recite that the morphogen activity is endogenous or the result of an exogenously provided morphogen. The claims also recite that the molecule that overcomes morphogen inhibition is a cytokine antagonist, more specifically a neuropoietic cytokine antagonist. The claims recite that the neuropoietic antagonist is a LIF antagonist or a CNTF antagonist. The claims also recite that the morphogen comprises an amino acid sequence having at least 70% homology with the C-terminal seven-cysteine skeleton of human OP-1, residues 330-431 of SEQ ID NO: 2. The claims recite that the molecule binds an endogenous ligand for a retinoid receptor. The claims

are directed to a molecule that is a cAMP-dependent messenger pathway inhibitor, specifically a protein kinase A inhibitor ((2-p-bromocinnamylaminoethyl)-isoquinolinesulfonamide).

Applicant's arguments (Paper No. 19, 11 March 2003), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) Applicant asserts that the specification has clearly provided ample *in vitro* examples of releasing morphogen inhibition, as well as examples of cAMP-dependent messenger pathway inhibitors that can be used for releasing morphogen inhibition.

Applicant's arguments have been fully considered but are not found to be persuasive. As discussed in the previous Office Action, the specification of the instant application teaches that LIF (cytokine) inhibits dendritic growth in cultured sympathetic neurons (pg 32, line 25). The specification teaches that the inhibitory effects of LIF on OP-1-induced dendritic growth is substantially reduced when 10-30 μg/ml of a polyclonal anti-LIF antibody is added to the medium (pg 27, lines 25-27; Figure 5). The specification also discloses that cultures of sympathetic neurons are treated with OP-1 for 5 days to induce dendritic growth and then LIF, antibody to gp130, or both agents are added on the 6^{th} day (pg 33, lines 1-10). The specification teaches that the antibody to the gp130 protein reduces the response to LIF (pg 33, Table III). Additionally, the specification discloses that cultures of sympathetic neurons are exposed to OP-1, OP-1 and CNTF, or OP-1 and LIF. The specification also teaches that some cultures are treated with PI-PLC before the CNTF and LIF treatments (pg 34, lines 1-6). The specification teaches that the CNTF-induced dendritic retraction is reduced by prior PI-PLC treatment (pg 33, lines 23-25; Figure 9). However, the specification of the instant application does not teach any methods or working examples that administer all possible molecules to a mammal and that

overcome morphogen inhibition to potentiate morphogen activity, promote neuronal cell growth, treat a disorder characterized by neuronal cell loss, or treat a neurodegenerative disorder. The specification does not disclose administering any molecules to a mammal that are cAMP-dependent messenger pathway inhibitors. Applicant has not indicated where in the specification support can be found for *in vitro* examples of releasing morphogen inhibition and examples of cAMP-dependent messenger pathway inhibitors that can be used for releasing morphogen inhibition.

(ii) Applicant argues that the rejection relates to *in vitro* and *in vivo* correlation and cites MPEP 2164.02. Applicant contends that either an *in vitro* model or *in vivo* model is sufficient to support the claimed methods as long as there is a correlation between the model and the claimed use. Applicant states that the using cultured neurons *in vitro* is a proper model that correlates with *in vivo* administering of morphogens. Applicant asserts that if a molecule is known to release morphogen inhibition *in vitro*, and leads to dendritic outgrowth as shown in Figure 5, a skilled artisan would expect that the same molecule would have the same effect on dendritic outgrowth *in vivo*. Applicant indicates that in Exhibits A and B (Guo et al., Neurosci Letters 245: 131-134, 1998 and Le Roux et al., Exp Neurol 160: 151-163, 1999, respectively), neurons are cultured *in vitro* using similar conditions and the effects of morphogens on these neurons are studied so that *in vivo* implications can be ascertained based on these studies. Applicant points out that the last paragraph of Exhibit B discusses the *in vitro* and *in vivo* correlation of these results based on other relevant findings in the field. Applicant also asserts that Exhibit C (WO 97/34626) demonstrates that morphogens can be administered intracisternally to experimental

animals (pg 35-36). Applicant states that pg 22, line 20 of the instant specification indicates that intracisternal administration is one of the possible routes of administering morphogens.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, the instant application does not teach any methods or working examples that administer all possible molecules to a mammal and that overcome morphogen inhibition to potentiate morphogen activity, promote neuronal cell growth, treat a disorder characterized by neuronal cell loss, or treat a neurodegenerative disorder *in vitro* or *in vivo*. There are also no facts or evidence in the art or the specification to indicate that cultured neurons *in vitro* is a proper model that correlates with *in vivo* administering of morphogens. Although the references of Exhibits A and B submitted by Applicant study the effects of OP-1 and dendritic growth *in vitro*, these references are not predictive of *in vivo* observations. Exhibit B (Le Roux et al.) indicates that the physiological significance of the morphogenic properties of OP-1 is emphasized due to its expression in the central nervous system (CNS) during development (pg 160, col 2). Le Roux et al. also disclose that BMPR-II is expressed at different times and locations in the brain, depending on the stage of development (pg 161, col 1). Le Roux et al. is only correlating the *in vitro* results with *in vivo* gene and protein expression during embryonic CNS development, which would obviously require dendritic growth. Le Roux et al. is not correlating *in vitro* studies with possible results of *in vivo* administration of OP-1 or BMPR-II. It is also noted that the experiments of Guo et al. and Le Roux et al. specifically contact neuronal cells with morphogens. All of the claims of the instant application do not recite the administration of a morphogen to a mammal, but rather, a composition comprising a molecule that overcomes morphogen inhibition. Le Roux et al. also utilize cerebral cortical neurons in

their experiments while Guo et al. utilize sympathetic neurons. The claims in the instant specification do not recite contact of a molecule with any specific neurons. Additionally, cells in a culture dish, particularly neurons, that exhibit growth and regenerative characteristics are not predictive of cells that are not capable of growth and regeneration *in vivo*. Therefore, the fact patterns of the references of Exhibits A and B cited by the Applicant and the claims of the instant rejection are significantly different.

It is also noted that a broad, reasonable interpretation of the claims encompasses treatment of such neurodegenerative disorders as Alzheimer's disease, Parkinson's disease, and Huntington's disease, among others, which have proven to be recalcitrant to treatment in the art (see for example, Halliday et al., Clin Exp Pharmacol Physiol 27: 1-8, 2000; Steece-Collier et al., Proc Natl Acad Sci USA 99(22): 13972-13974, 2002; Feigin et al. Curr Opin Neurol 15: 483-489, 2002). Hence, undue experimentation would be required of the skilled artisan to promote neuronal cell growth, treat a disorder characterized by neuronal cell loss, and treat a neurodegenerative disorder by administration of all possible molecules that overcome morphogen inhibition.

Furthermore, one skilled in the art would not be able to predict that *in vitro* results with morphogens are predictive of *in vivo* results. For example, the state of the art is such that for the nervous system, hypotheses that hold well *in vitro* rarely, if ever, translate directly into the clinic (Lo, DC, Current Drug Discovery, June 2002, pg 27-30). Lo et al. discusses that models for neural processes and pathologies become baroque in attempting to account for the multiplicity of neuronal interactions in the basic neural systems (pg 28, ¶ 3). Lo adds that hypotheses generated out of neural modeling systems are rarely robust enough to be predictive of drug intervention

targets (pg 27, ¶ 3). Additionally, Chung et al. (Circulation 107: 3133-3140, 2003) discloses that infliximab, a recombinant immunoglobulin G1-κ human-murine chimeric monoclonal antibody, specifically binds to and neutralizes the soluble TNFα homotrimer and its membrane bound precursor (pg 3133, ¶ 2 through top of pg 3134). However, when patients with moderate to severe heart failure were administered infliximab (10 mg/kg per infusion), they did not show an improvement in any of a broad range of objective and subjective clinical assessments (pg 2137, col 1-2). Chung et al. also reports that treatment of patients receiving high doses of infliximab was associated with worsening clinical status, an increased likelihood of hospitalization, and a high frequency of worsening heart failure, during and 5 months after cessation of therapy (pg 2137, col 2). Chung et al. indicates that infliximab failed to produce clinical benefits even though the drug exerted its expected biological effects (pg 3137, col 2). Clari et al. (Circulation 105(21) : E183, 2002) even report that there have even been at least 8 patient deaths among 150 receiving infusions of infliximab for chronic heart failure. The art teaches that the results of these infliximab clinical trials are different from those previously reported with the use of TNFα antagonists in experimental models of heart failure. For example, administration of the soluble TNFα receptor etanercept eases adverse cardiac effects associated with the infusion of TNFα in rats (Chung et al., pg 3138, first full paragraph). Chung et al. indicate that favorable results with therapeutic agents in experimental models of heart failure, for example, have not been replicated in controlled clinical trials (pg 3138, first full paragraph). Therefore, one skilled in the art would not expect to predict that *in vitro* results with morphogens or any other molecule are predictive of *in vivo* results.

Finally, the skilled artisan must still resort to trial and error experimentation to determine the optimal dosage, duration, and mode of administration of all possible molecules that overcome morphogen inhibition. Such trial and error experimentation is considered undue. Although the reference of Exhibit C administers OP-1 intracisternally to rats and the specification refers to intracisternal administration as one of many possible routes of administering morphogens, the results of the methods recited in the claims of the instant application are unpredictable and complex when combined with the step of administering any molecule to potentiate morphogen activity, promote neuronal cell growth, treat a disorder characterized by neuronal cell loss, and treat a neurodegenerative disorder. The specification discloses numerous methods of administration of the claimed composition at pages 22-24. However, this is not adequate guidance, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Also, the claimed methods do not specifically recite that the composition is administered to the mammal intracisternally. The claims encompass any method of administration and any dosage for any length of time.

(iii) Applicant argues that the specification (pg 20) teaches a method for identifying and testing inducers competent to modulate the levels of endogenous morphogens in a given tissue is described in detail in WO 93/05172 and WO 93/05751. Applicant summarizes that candidate molecules can be identified and tested by incubation *in vitro* with a test tissue or cells or a cultured cell line derived therefrom, for a time sufficient to allow the compound to affect the production of a morphogen produced by the cells of that tissue. Applicant contends that based on this teaching, the skilled artisan could readily identify a potential molecule that overcomes

morphogen inhibition, and the dose and duration of achieving the effect *in vitro*. Applicant argues that the *in vitro* results will guide a skilled artisan to determine a proper dose and duration for *in vivo* use, using routine experimentation. Applicant submits that a skilled artisan would readily be able to determine the optimal dosage and duration for individual patients.

Applicant's arguments have been fully considered but are not found to be persuasive. The specification of the instant application outlines prophetic procedures for administering all possible molecules to a mammal and overcoming morphogen inhibition to potentiate morphogen activity, promote neuronal cell growth, treat a disorder characterized by neuronal cell loss, or treat a neurodegenerative disorder (pg 2, 22-24, 34-41). However, this is not adequate guidance, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Additionally, as was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). The present invention is unpredictable and complex wherein one skilled in the art may not necessarily potentiate morphogen activity, promote neuronal cell growth, treat a disorder characterized by neuronal cell loss, or treat a neurodegenerative disorder by administration of a molecule that overcomes morphogen inhibition to a mammal. Although the claimed methods may utilize routine administration techniques, the results of the methods are unpredictable and complex when combined with the step of administering any molecule.

Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to potentiate morphogen activity, promote neuronal cell growth, treat a disorder characterized by neuronal cell loss, and treat a neurodegenerative disorder and to determine the optimal dosage, duration, and mode of administration of all possible molecules, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, the unpredictability of the effects of administering a molecule to a mammal, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

35 USC § 112, second paragraph

8. Claims 1-12, 16-19, and 22-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. Claims 2-3, 8-12, 16-19, and 22-26 are indefinite because the claims do not have a step that clearly relates back to the preamble. For example, there is no step indicating how administration of a molecule potentiates morphogen activity. There is no step indicating how administration of a molecule promotes neuronal cell growth, treats a disorder characterized by neuronal cell loss, or treats a neurodegenerative disorder. The basis for this rejection is set forth at pg 8-9 of the previous Office Action (Paper No. 17, 13 November 2002).

Applicant's arguments (Paper No. 19, 11 March 2003), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant asserts that the molecule administered is not just about any molecule, but rather a molecule "that overcomes morphogen inhibition". Applicant argues that said molecule by definition would release inhibitory effects on morphogen activity and potentiate any morphogen-stimulated activity.

Applicant's arguments have been fully considered but are not found to be persuasive. As mentioned above, there is no step indicating that the administration of a molecule promotes neuronal cell growth, treats a disorder characterized by neuronal cell loss, or treats a neurodegenerative disorder. Please note that this issue could be overcome by amending the last line of the claims to recite, for example, "...thereby to potentiate growth-promoting effects of endogenous morphogens to promote neuronal cell growth (or treat a disorder characterized by neuronal cell loss or to treat a neurodegenerative disorder.)

10. The term "morphogen activity" in claims 1-12, 16-19, and 22-26 is a relative term which renders the claims indefinite. The term "morphogen activity" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It cannot be determined if "morphogen activity" means for example, inducing the migration, proliferation and differentiation of progenitor cells, inducing bone morphogenesis, or repairing non-chondrogenic tissues. The basis for this rejection is set forth at pg 8-9 of the previous Office Action (Paper No. 17, 13 November 2002).

Applicant's arguments (Paper No. 19, 11 March 2003), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant asserts that the instant claimed invention is partly based on the general discovery that morphogen-stimulated activity may be suppressed due to the presence of certain inhibitors of morphogen activity. Applicant contends that these inhibitors are expected to inhibit all aspects of morphogen activity. Applicant argues that the claims are to be their broadest plain meaning, and in this case, morphogen-stimulated biological activity. Applicant submits that the previous Office Action failed to present what activity might or might not be considered to be within the scope of the term.

Applicant's arguments have been fully considered but are not found to be persuasive. Although Applicant need not explicitly recite every feature of the invention in the claims, the metes and bounds of the term "morphogen activity" is not clearly set forth in the claims or the instant application. Any and all activities may be encompassed by the term "morphogen activity" and in the previous Office Action, Examiner suggested that such activities may include, inducing the migration, proliferation and differentiation of progenitor cells, inducing bone morphogenesis, or repairing non-chondrogenic tissues, among others. It is not clear from the specification or the claims what activities are or are not encompassed by this term.

11. The term "morphogen inhibition" in claims 1-12, 16-19, and 22-26 is a relative term which renders the claims indefinite. The term "morphogen inhibition" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It cannot be determined if "morphogen inhibition" means for example, inhibiting the migration, proliferation and differentiation of progenitor cells, inhibiting bone morphogenesis, or inhibiting

the repair of non-chondrogenic tissues. The basis for this rejection is set forth at pg 8-9 of the previous Office Action (Paper No. 17, 13 November 2002).

Applicant's arguments (Paper No. 19, 11 March 2003), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant contends that the term "morphogen inhibition" can be interpreted based on its plain meaning. Applicant states that such degrees of inhibition, like the degree of activity, is unnecessary to define inhibition. Applicant indicates that a skilled artisan would readily understand and the plain meaning of inhibition in view of the specification.

Applicant's arguments have been fully considered but are not found to be persuasive because it is inappropriate to read limitations in the specification into the claims. The claims must independently define the invention for which patent protection is sought. Therefore, the claims are still rejected as being indefinite because the claims do not recite a clear definition of the term "morphogen inhibition".

Conclusion

No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:30-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 872-9305.

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER

BEB
Art Unit 1647
August 12, 2003